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Monitoring anti-interleukin 6 receptor antibody treatment for rheumatoid arthritis by quantitative magnetic resonance imaging of the hand and power Doppler ultrasonography of the finger

Abstract

Objectives: To compare quantitative magnetic resonance imaging (MRI) and power Doppler ultrasonography (PDUS) with conventional measures of disease activity in rheumatoid arthritis (RA) patients with the anti-interleukin 6 (anti-IL 6) receptor antibody tocilizumab in terms of responsiveness at a few months to disease activity and ability to predict structural damage at 1 year.

Methods: A cohort of patients with RA (N = 29) was evaluated clinically including disease activity score 28 (DAS28)and by semiquantitative (SQ-) and quantitative (Q-) PDUS (bilateral metacarpophalangeal joints) and MRI (one hand and wrist) at initiation of treatment with anti-IL 6 receptor antibody agents and after 2 and 5 months. Conventional radiography for both hands and wrists was performed at baseline and at 12 months. Responsiveness was assessed by standardized response means (SRM). Areas under the curve (AUC) for measures at baseline, 2 and 5 months were correlated with structural damage at one year.

Results: Among the laboratory and clinical parameters, DAS28-ESR was the most responsive with a large effect size of SRM. Structural damage progressions for radiography and MR erosion were correlated with AUC of MR bone erosion and Q-PDUS, respectively.

Conclusions: In the evaluation of disease activity in RA patients in the first few months after starting anti-IL 6 receptor antibody tocilizumab treatment, the semi-quantitative MR bone erosion score of the hand and quantitative value for power Doppler signal in the finger joint were both responsive and predictive of structural damage progression at 1 year.

Key Words

anti-interleukin 6 receptor antibody; rheumatoid arthritis; quantitative analysis; magnetic resonance imaging; power Doppler ultrasonography

Intriduction

Tocilizumab is a humanized anti-interleukin 6 (anti-IL 6) receptor antibody [1] which has been demonstrated to improve the signs and symptoms of RA and prevent radiographic progression in previous clinical trials [2-8]. Structural damage in RA has traditionally been assessed by conventional radiography and disease activity by individual core set variables as well as different composite indices such as the disease activity score (DAS), simplified disease activity index (SDAI) and clinical disease activity index (CDAI) [9-12]. In recent years, magnetic resonance (MR) imaging and ultrasonography (US) have increasingly been used as outcome measures in clinical trials of RA [13-16]. Quantitative analysis in magnetic resonance imaging and US theoretically have advantages over semi-quantitative analysis in measuring the response to therapeutic agents, as the former can reflect a change in inflammatory activity more sensitively and objectively.

The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) has developed procedures to reach a consensus on which measures to apply in clinical trials [17]. The main objective in clinical trials is the measurement of change (e.g., monitoring treatment effect) and, in this setting, the concept of

responsiveness may be the most important characteristic of an outcome measure when deciding which particular instrument to use in a clinical trial [18, 19]. A more responsive measure has obvious advantages including reduction of sample sizes for clinical studies. The most accepted means to measure therapeutic effect is OMERACT-RAMRIS (RA MRI scoring system). The RAMRIS consists of semi-quantitative assessment of bone erosion, bone marrow edema, and synovitis, which is sensitive to change over weeks as well as months [20-22]. RAMRIS is being used increasingly in trials of biological agents to measure changes in these markers for disease activities. Recent work has shown that in the cohort of patients receiving tumor necrosis factor alpha (TNFα) treatment, the MR total inflammation score displayed superior responsiveness to conventional measures of disease activity, indicating its promise as an outcome measure in clinical studies and for clinical practice [23]. However, less is known about the responsiveness of imaging measures during intervention with anti-IL6 treatment. The main objective of this study was to assess inflammatory changes in RA patients during the first few months of anti-IL6 treatment by MR imaging and power Doppler ultrasonography (PDUS) measures, using conventional semi-quantitative and newly introduced

quantitative assessment. We compared these measures with conventional measures of disease activity in terms of their responsiveness to disease activity and ability to predict structural damage at 1 year.

Materials and Methods

Patients

This prospective study was approved by the institutional review board; patients and control subjects gave written informed consent. In the prospective study to investigate the value of analysis on image and clinical parameters in rheumatoid patients treated with tocilizumab, 29 consecutive patients were available for testing at baseline, and 2- and 5-month follow-ups with PDUS and MR studies including non-contrast and contrast imaging sequences. Radiographs of the hands were evaluated for baseline and follow-up at 12 months when available. All patients satisfied the American College of Rheumatology revised 1987 criteria for RA [24]. A portion of our patient population has been previously reported [25].

Tocilizumab therapy

Each patient received intravenous injections of monotherapy (8 mg/kg intravenously every 4 weeks). The dose, type, and combination of Disease-Modifying Antirheumatic Drugs (DMARDs) and/or immunosuppressants could vary according to disease activity at the discretion of the treating physician. The kinds and doses of other drugs that each patient was taking were not changed during the study period.

Clinical assessment

Clinical evaluation was performed for each patient by one of the five rheumatologists (K.T, S.M, M.M, F.J, and K.Y), all of whom were blinded to the imaging findings.

Laboratory assessment

Serum markers of inflammation, C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR) were obtained on the same day as MR imaging.

Disease activity assessment

In the assessment of disease activity, DAS28-ESR (erythrocyte sedimentation rate) was used. The DAS28-ESR is provided as DAS28-ESR = $0.555\times(TJC)^{0.5} + 0.284\times(SJC)^{0.5} + 0.7\times LN(ESR) + 0.0142\times(VAS)$, indicating how active the rheumatoid arthritis was at the moment [26], where TJC is the tender joint count; SJC is the swollen joint count; and VAS is the visual analog scale.

PDUS assessment.

PDUS was performed at baseline, and at 2 and 5 months by one of the three ultrasonographers (H.M, S.F, N.A) specializing in musculoskeletal US, who have 2, 7, and 8 years of experience, respectively. They were blinded to other clinical information. A 13-MHz linear array transducer was used (HITACHI EUP-L34P, HITACHI, Tokyo, Japan). Pulse Doppler settings were standardized for the detection of synovial blood flow by adjusting color gain, pulse repetition, and flow optimization parameters according to the method in a previous study [27]. Power Doppler settings (75 dB dynamic range, medium persistence, medium frame rate, low wall filter, 1,300 Hz pulse repetition frequency, medium vein flow optimization, 1,300 Hz speed velocity) were identical throughout the

examinations. Room temperature was kept at 25°C. The patients were positioned comfortably, and examinations were started after 10 minute's stabilization of pulse rate. The scanning technique on each finger was standardized and fixed: for the 1st – 5th metacarpophalangeal (MCP) joints, scanning was performed in the longitudinal plane over the dorsal surface of the joint with light skin pressure. The basic scanning technique followed the EULAR guidelines [28] The synovial vascular area with the most pronounced power Doppler activity was identified from the cine-loop and stored. The PDUS images were recorded on the hard drive of the ultrasonographic machine. All examinations were completed within 15 minutes. Semi-quantitative grading has been described in previous studies (0 = absence of signal, 1 = single vessel dots, 2 = vessel dots over less than half of the synovial area, 3 = vessel dots over greater than half of the synovial area)[29]. This grade for each joint was defined as the joint grade for the power Doppler signal (JGPD). Representative images for each JGPD are shown in Figure 1. The sum of JGPD for 10 MCP (bilateral 1-5 MCP joints) joints was defined as JGPD-10. Quantitative PDUS is the number of vascular flow pixels in the region of interest (ROI). The ROI was a standardized box type (5mm × 10mm), which was located to contain as many of

the vascular flow pixels as possible. Vascular flow pixels in the ROI were measured automatically using the vascularity mode of the ultrasonographic machine (HITACHI EUB-6500, HITACHI, Tokyo, Japan). The joint index for the power Doppler signal (JIPD) represented the vascular flow pixels in the ROI for each joint (Figure 2). The sum of JIPD for 10 MCP (bilateral 1-5 MCP joints) joints was defined as JIPD-10.

MR imaging and assessment

MR images of both hands were taken at baseline and follow-up using the 1.5-T system (Signa Exicite ver. 12, GE Medical Systems, Milwaukee, WI, USA) with a cardiac coil. During the examination, patients were placed in the supine position with both hands on the abdomen, which were covered by an anterior segment of the cardiac coil. The following images were obtained for both hands: T1-weighted coronal imaging (TR/TE 500/11 ms, FOV 30 cm, matrix 256 × 192, 20 slices, slice thickness 3 mm, gap 0.4 mm, number of excitations 2), STIR coronal imaging (TR/TE/TI 3600/25/150 ms, FOV 30 cm, matrix 256 × 224, 20 slices, slice thickness 4 mm, gap 1 mm), STIR axial imaging (TR/TE/TI 3600/25/150 ms, FOV 32 cm, matrix 256 × 224, 20 slices, slice thickness 4 mm,

gap 0 mm), and post contrast T1-weighted coronal imaging (TR/TE 500/11 ms, FOV 30 cm, matrix 256 × 192, 20 slices, slice thickness 3 mm, gap 0.4 mm). Bolus gadopentetate dimeglumine (Gd-DTPA), (Magnevist 0.1 mmol/kg body weight; Bayer. Schering Pharma, Osaka, Japan) was administered at 1 ml/sec via a 21-G indwelling needle inserted into an antecubital fossa vein, 3 minutes before acquisition of postcontrast images. Data were transferred from the MRI console to a Digital Imaging and Communications in Medicine (DICOM) viewer (Toshiba Medical Systems Corporation, Tochigi, Japan) and a workstation (Advantage Windows workstation, GE Medical Systems, Milwaukee, WI, USA) for quantitative analysis respectively.

OMERACT-RAMRIS (confined to the wrist) was carried out on both wrists of all subjects by an experienced radiologist (KT) who was blinded to other clinical information [22] The scoring was repeated twice with a 2-month interval, and intraobserver variability was assessed.

We introduced a simple volumetry method using STIR image data for the pannus by setting the muscle signal as a threshold in the pilot study [25]. Briefly, the pannus was visualized as a high signal on STIR images; on the contrary, normal muscle was low signal intensity on STIR. We set a region of interest

(ROI) of 10 mm^2 in the left adductor pollicis muscle on a STIR image, and measured the average signal in the ROI for a standard for the threshold (Figure 3a). The volume of the signal was measured to cover the wrists and MCP joints (distal ulna, distal radius, carpal bones, metacarpal bones, 1-5 matacarpophalangeal joints, and soft tissue); 1 cm proximal to the wrist joints and 1 cm distal to the MCP joints (Figures 3b and 3c). The coverage of the volumetry was expanded for this study to include the MCP joints in addition to the wrists. We set 1.5 times the muscle signal as the threshold, and the volume of abnormal signals was obtained (Figure 3d); we defined this volume as V_MRI. This volumetry was carried out by 2 MR technologists independently.

Radiography and assessment.

Plain radiographs of hands were obtained at baseline and at the 1-year follow-up. Radiological assessments were examined for bilateral hands twice with a 2-month interval according to the Genant-modified Sharp score by a radiologist (KT) who was blinded to other clinical information [30].

Statistical analysis

Statistical analyses were calculated with the use of the Excel program (Microsoft, Redmond, WA, USA) and MedCalc program 10.4.5.0 (MedCalc Software, Mariakerke, Belgium). Intra- and inter-observer reliabilities were estimated using calculations of intraclass correlation coefficients (ICC). The ICC ranged from -1 to +1. ICC values are interpreted as follows: <0.40, poor to fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, substantial agreement; 0.81 to 1.00, almost perfect agreement (20). Quantitative variables (clinical, laboratory, PDUS, MR imaging, and RAMRIS) were given as median, interquartile range, and range. All statistical analyses were undertaken using the MedCalc program 10.4.5.0 (MedCalc Software, Mariakerke, Belgium). The standardized response mean (SRM) was calculated as the ratio of the mean change in the measure and the standard deviation of the mean change scores. The term ‘‘responsiveness’’ denotes the magnitude of change or sensitivity to change over time. To quantify responsiveness, several effect sizes have been proposed as estimates of the amount of change detected with an instrument, resulting in a wide variety of effect size indices [31-33]. It is not yet known which of these statistics is the better for assessing responsiveness, although there is some evidence to suggest that it is better to estimate the magnitude of the

change using the SD of the change score (i.e., SRM) in the denominator compared with the SD at baseline (i.e., effect size) [34-36]. We therefore chose to assess responsiveness using SRM. There is no universal agreement on how to interpret the magnitude of the SRMs, but in most cases the thresholds introduced by Cohen for effect sizes (ES) were applied: “trivial” (ES < 0.20), “small” (0.20 ≤ ES < 0.50), “moderate” (0.50 ≤ ES < 0.80) or “large” (0.80 ≤ ES) [31]. Correlations between clinical, laboratory, PDUS, MR imaging and radiographic parameters were analyzed by Pearson’s or Spearman’s rank correlation test according to the variable distribution. The course of the process variables was obtained by calculating time-integrated values (TIV) using the area-under-the-curve method [37]. Any p value less than 0.05 was considered statistically significant.

RESULTS

Measured quantities, abbreviations, and possible ranges are shown in Table 1. The demographic characteristics and immunological/therapeutic status are listed in Table 2, The clinical measures of disease activity and imaging measures at baseline, and 2 and 5 months are summarized in Table 3a and 3b,

respectively.

Both intra-observer reliability for RAMRIS and Genant-modified Sharp score by a radiologist were in almost perfect agreement (ICC = 0.840 and 0.9137, respectively). Inter-observer reliability for V_MRI between 2 technologists showed substantial agreement (ICC = 0.7449).

Representative MR and PDUS images to show the therapeutic effect are shown in Figures 4 and 5, respectively.

The mean changes and SRMs of the measures from baseline at 2 and 5 months are presented in Table 4. At the 2-month follow-up there was a marked (moderate to large) treatment response in clinical measures, and the same tendency was observed at 5 months. The SRMs for imaging measures were trivial to small at 2 and 5 months, except that for MR erosion, which showed a moderate response. The SRM for QMRI and QPDUS had negative values, and they were more sensitive than semiquantitative imaging measures (small versus trivial) at 2 months. RAMRIS synovitis, SQPDUS, and PDUS had small responses with negative values at 5 months.

Table 5 shows the correlation between the measures and structural damage/damage progression assessed with radiography and MRI. Structural

damage progressions for radiography were correlated with TIV of MR bone erosion ($r = 0.6476$, $p = 0.0167$). Structural damage progressions for MR erosion were correlated with TIV of JIPD-10 ($r = 0.5573$, $p = 0.0478$). The TIV of DAS28-ESR was not correlated with 1-year structural damage progression for either radiography or MR erosion.

DISCUSSION

This study has shown that conventional measures of disease activity provide superior responsiveness to imaging measures of inflammation in patients with RA treated with anti-IL 6 medication. However, conventional measures of disease activity had poor correlation with 1-year structural destruction progression. Traditional treatment goals for patients with RA include reduction of inflammation (i.e., relieving signs and symptoms), improving physical functioning and inhibiting the progression of joint damage. Evaluation of disease activity in RA is not easy, and no single marker can reflect all these aspects. A reliable measure should show good responsiveness and allow prediction of future structural damage. While prescribing the anti-TNFα medication for chronic RA patients, Haavardsholm, et al. reported that the MR total inflammation score

displayed superior responsiveness to conventional measures of disease activity, and may be a promising outcome measure in clinical studies and for clinical practice [23]. However, we have observed that this finding is not applicable to patients with RA treated with anti-IL 6 medication.

In semi-quantitative MR measures, MR bone erosion may be useful with moderate responsiveness at month 5 and with correlation between radiography changes. Other MR measures are not useful: MR synovitis showed no and small responsiveness at month 2 and 5, respectively, and there was no statistically significant correlation between future radiography or MR bone lesion progression. Quantitative MR imaging showed small and trivial responsiveness at month 2 and 5, respectively, and there was no statistically significant correlation with future radiography or MR bone lesion progression. Quantitative MR imaging was shown to reflect the improvement of MR synovitis and erosion according to the previous study.

In PDUS measures, quantitative PDUS was more responsive than semi-quantitative PDUS (small versus trivial) at month 2, and both were small at month 5. The correlation of the cumulative PDUS measure with MR bone lesions was statistically significant. This may show that quantitative PDUS is more useful

than semi-quantitative PDUS measures. A comparison of the two methods revealed that the quantitative PDUS method strongly correlates with the semi-quantitative PDUS in terms of RA assessment [27, 38]; moreover, the change of synovial vascularity in a single finger joint determined by the quantitative PDUS could numerically predict its radiographic progression in RA patients treated with methotrexate [39]. This study may constitute further evidence to support the suggestion that quantitative PDUS is more sensitive to changes in synovial activity and thus predictive of future structural damage.

The present study included a rather small number of patients and had no control/placebo group; the number of participants was even smaller for the 1-year follow-up data. However, all patients had active disease, and the intervention with a potent drug, combined with a very extensive data collection of outcome measures, allowed comparisons of the responsiveness of these measures in a real-life setting. Another limitation may be that a relatively larger field of view was selected for MR data acquisition, possibly resulting in decreased spatial resolution compared with parameter setting for a dedicated joint study. Thus, this study may have underestimated the value of MR imaging in terms of responsiveness and prediction of future progression in structural

damage during treatment.

In this cohort of patients receiving the anti-IL 6 receptor antibody tocilizumab, we have shown that conventional measures are responsive but less reflective of future bone destruction than image analysis. In the evaluation of disease activity in RA patients within one year of beginning treatment with the anti-IL 6 receptor antibody tocilizumab, MR bone erosion and quantitative PDUS may be both responsive and predictive of structural damage progression at 1 year.

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Conflict of Interest

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References

1. Nishimoto N, Kishimoto T, Yoshizaki K. Anti-interleukin 6 receptor antibody treatment in rheumatic disease. Ann Rheum Dis. 2000; 59 Suppl 1:i21-27.

2. Choy EH, Isenberg DA, Garrood T, Farrow S, Ioannou Y, Bird H, et al. Therapeutic benefit of blocking interleukin-6 activity with an anti-interleukin-6 receptor monoclonal antibody in rheumatoid arthritis: a randomized, double-blind, placebo-controlled, dose-escalation trial. Arthritis Rheum. 2002; 46(12):3143-3150.

3. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008; 67(11):1516-1523.
4. Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum. 2008; 58(10):2968-2980.
5. Maini RN, Taylor PC, Szechinski J, Pavelka K, Broll J, Balint G, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum. 2006; 54(9):2817-2829.
6. Nishimoto N, Yoshizaki K, Maeda K, Kuritani T, Deguchi H, Sato B, et al. Toxicity, pharmacokinetics, and dose-finding study of repetitive treatment with the humanized anti-interleukin 6 receptor antibody MRA in rheumatoid arthritis. Phase I/II clinical study. J Rheumatol. 2003; 30(7):1426-1435.
7. Nishimoto N, Yoshizaki K, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum. 2004; 50(6):1761-1769.
8. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008; 371(9617):987-997.
9. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther. 2005; 7(4):R796-806.
10. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum. 1993; 36(6):729-740.
11. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford). 2003; 42(2):244-257.
12. van der Heijde DM, van 't Hof M, van Riel PL, van de Putte LB. Development of a

disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol. 1993; 20(3):579-581.
13. Iagnocco A, Filippucci E, Perella C, Ceccarelli F, Cassara E, Alessandri C, et al. Clinical and ultrasonographic monitoring of response to adalimumab treatment in rheumatoid arthritis. J Rheumatol. 2008; 35(1):35-40.
14. Jarrett SJ, Conaghan PG, Sloan VS, Papanastasiou P, Ortmann CE, O'Connor PJ, et al. Preliminary evidence for a structural benefit of the new bisphosphonate zoledronic acid in early rheumatoid arthritis. Arthritis Rheum. 2006; 54(5):1410-1414.
15. Ostergaard M, Duer A, Nielsen H, Johansen JS, Narvestad E, Ejbjerg BJ, et al. Magnetic resonance imaging for accelerated assessment of drug effect and prediction of subsequent radiographic progression in rheumatoid arthritis: a study of patients receiving combined anakinra and methotrexate treatment. Ann Rheum Dis. 2005; 64(10):1503-1506.
16. Ribbens C, Andre B, Marcelis S, Kaye O, Mathy L, Bonnet V, et al. Rheumatoid hand joint synovitis: gray-scale and power Doppler US quantifications following anti-tumor necrosis factor-alpha treatment: pilot study. Radiology. 2003; 229(2):562-569.
17. Boers M, Brooks P, Strand CV, Tugwell P. The OMERACT filter for Outcome Measures in Rheumatology. J Rheumatol. 1998; 25(2):198-199.
18. Bellamy N. Clinimetric concepts in outcome assessment: the OMERACT filter. J Rheumatol. 1999; 26(4):948-950.
19. Bellamy N, Kirwan J, Boers M, Brooks P, Strand V, Tugwell P, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. J Rheumatol. 1997; 24(4):799-802.
20. Dohn UM, Skjodt H, Hetland ML, Vestergaard A, Moller JM, Knudsen LS, et al. No erosive progression revealed by MRI in rheumatoid arthritis patients treated with etanercept, even in patients with persistent MRI and clinical signs of joint inflammation. Clin Rheumatol. 2007; 26(11):1857-1861.
21. Lisbona MP, Maymo J, Perich J, Almirall M, Perez-Garcia C, Carbonell J. Etanercept reduces synovitis as measured by magnetic resonance imaging in patients with active rheumatoid arthritis after only 6 weeks. J Rheumatol. 2008; 35(3):394-397.
22. Ostergaard M, Edmonds J, McQueen F, Peterfy C, Lassere M, Ejbjerg B, et al. An introduction to the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas. Ann Rheum Dis. 2005; 64 Suppl 1:i3-7.
23. Haavardsholm EA, Ostergaard M, Hammer HB, Boyesen P, Boonen A, van der Heijde D, et al. Monitoring anti-TNFalpha treatment in rheumatoid arthritis: responsiveness of magnetic resonance imaging and ultrasonography of the dominant wrist

joint compared with conventional measures of disease activity and structural damage. Ann Rheum Dis. 2009; 68(10):1572-1579.
24. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988; 31(3):315-324.
25. Kamishima T, Tanimura K, Aoki Y, Kosaka N, Shimizu M, Matsuhashi M, et al. Simplified approach to MR image quantification of the rheumatoid wrist: a pilot study. Skeletal Radiol.
26. van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum. 1996; 39(1):34-40.
27. Kamishima T, Tanimura K, Henmi M, Narita A, Sakamoto F, Terae S, et al. Power Doppler ultrasound of rheumatoid synovitis: quantification of vascular signal and analysis of interobserver variability. Skeletal Radiol. 2009; 38(5):467-472.
28. Backhaus M, Burmester GR, Gerber T, Grassi W, Machold KP, Swen WA, et al. Guidelines for musculoskeletal ultrasound in rheumatology. Ann Rheum Dis. 2001; 60(7):641-649.
29. Meenagh G, Filippucci E, Delle Sedie A, Riente L, Iagnocco A, Epis O, et al. Ultrasound imaging for the rheumatologist. XVIII. Ultrasound measurements. Clin Exp Rheumatol. 2008; 26(6):982-985.
30. Genant HK, Jiang Y, Peterfy C, Lu Y, Redei J, Countryman PJ. Assessment of rheumatoid arthritis using a modified scoring method on digitized and original radiographs. Arthritis Rheum. 1998; 41(9):1583-1590.
31. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed ed. New Jersey: Lawrence Erlbaum, 1988.
32. Guyatt G, Walter S, Norman G. Measuring change over time: assessing the usefulness of evaluative instruments. J Chronic Dis. 1987; 40(2):171-178.
33. Liang MH, Fossel AH, Larson MG. Comparisons of five health status instruments for orthopedic evaluation. Med Care. 1990; 28(7):632-642.
34. Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. Med Care. 1989; 27(3 Suppl):S178-189.
35. Middel B, van Sonderen E. Statistical significant change versus relevant or important change in (quasi) experimental design: some conceptual and methodological problems in estimating magnitude of intervention-related change in health services

research. Int J Integr Care. 2002; 2:e15.
36. Wright JG, Young NL. A comparison of different indices of responsiveness. J Clin Epidemiol. 1997; 50(3):239-246.
37. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. BMJ. 1990; 300(6719):230-235.
38. Fukae J, Shimizu M, Kon Y, Tanimura K, Matsuhashi M, Kamishima T, et al. Screening for rheumatoid arthritis with finger joint power Doppler ultrasonography: quantification of conventional power Doppler ultrasonographic scoring. Mod Rheumatol. 2009; 19(5):502-506.
39. Fukae J, Kon Y, Henmi M, Sakamoto F, Narita A, Shimizu M, et al. Change of synovial vascularity in single finger joint assessed by power Doppler sonography correlated with radiographic change in rheumatoid arthritis: Comparative study of novel quantitative score with semi-quantitative score. Arthritis Care Res (Hoboken).

Quantity that was measured	Abbreviation	Possible range of values
Visual analog scale for patient's overall assessment of disease activity (mm)	VAS	0-100
Tender joint count	TJC	0-28
Swollen joint count	SJC	0-28
Erythrocyte sedimentation rate (mm)	ESR	NA
C-reactive protein (mg/dl)	CRP	NA
28-joint Disease Activity Score-ESR	DAS28-ESR	0-10
Joint grade for power Doppler signal	JGPD	0-3
Sum of JGPD for 10 joints	JGPD-10	0-30
Joint index for power Doppler signal	JIPD	0-100
Sum of JIPD for 10 joints	JIPD-10	0-100
RA MRI scoring system (total)	RAMRIS (total)	0-410
RA MRI scoring system (synovitis)	RAMRIS (synovitis)	0-42
RA MRI scoring system (bone erosion)	RAMRIS (bone erosion)	0-230
RA MRI scoring system (bone edema)	RAMRIS (bone edema)	0-138
The volume of abnormal MR signals(cm3)	V_MRI	NA

Table 1 Measured quantities, abbreviations, and possible ranges

RA; rheumatoid arthritis, MRI; magnetic resonance imaging, NA; not applicable

Age, mean (range) years	61 (27-74)
Sex, female/male	27/2
RF positive, yes/no/unknown	17/4/8
Prior use of DMARDs, yes/no	23/6
Prior use of other biologics, yes/no	15/14
Duration of symptoms, median (range) months	8 (1-34)

Table 2 The demographic characteristics and immunological/therapeutic status at baseline

RF; rheumatoid factor, DMARDs; Disease-Modifying Antirheumatic Drugs

Parameters	Month 0	Month 2	Month 5
VAS (%)	50	40	26
	35.5	22.5	11
	21-90	2-82	0-78
	27	23	23
TJC	6	3	2
	3.5	1.5	1
	1-16	0-9	0-13
	27	23	23
SJC	2	1	0
	2	0	0
	0-11	0-10	0-6
	27	23	23
ESR (mm)	44	8	8
	29	8	7
	15-139	5-118	5-120
	29	29	29
CRP (mg/dl)	1.49	0.1	0.1
	0.44	0.1	0.1
	0.1-13.88	0.1-5.9	0.1-11.7
	29	28	29
DAS28-ESR	5.38	3.49	3.02
	4.81	2.875	2.01
	3.1-6.95	1.39-6.07	1.424.65
	27	23	23

Table 3a Clinical measures of disease activity at baseline and 2 and 5 months

From top to bottom, values are the median, range, 1st quartile and number of patients included. See Table 1 for abbreviations.

Parameters	Month 0	Month 2	Month 5
JGPD-10	6	4	4
	0	0	0
	0-128	0-148	0-110
	29	29	29
JIPD-10	14	3	5
	0	0	0
	0-459	0-610	0-405
	29	29	29
RAMRIS	26	26	26
(total)	15	14	14
	0-123	0-123	0-123
	27	27	27
RAMRIS	11.5	11.5	11.5
(synovitis)	9.25	8.5	9
	0-27	0-25	0-25
	26	26	26
RAMRIS	10.5	10.5	11.5
(bone erosion)	5.25	5	5.25
	0-103	0-103	0-103
	26	26	26
RAMRIS	0	0	0
(bone edema)	0	0	0
	0-24	0-24	0-23
	26	26	26
V_MRI (ml)	31.2	27.9	34.3

22.1	19	19.8
16.4-107	5-89.2	4.3-147.6
29	29	29

Table 3b The imaging measures at baseline, and 2 and 5 months

From top to bottom, values are the median, range, 1st quartile and number of patients included. See Table 1 for abbreviations.

	2 months		5 months	
	Changes (95% CI)	SRM	Changes (95% CI)	SRM
US				
JGPD-10	-1.5172 (-4.9295 to 1.8950)	-0.1691	-4.4138 (-10.8831 to 2.0555)	-0.2595
JIPD-10	-9.3793 (-26.9144 to 8.1557)	-0.2034	-16.7586 (-37.5682 to 4.0510)	-0.3063
MRI				
RAMRIS (Synovitis)	0.0000 (-0.2383 to 0.2383)	0	-0.4400 (-1.0714 to 0.1914)	-0.2876
RAMRIS (BME)	0.4800 (-0.5107 to 1.4707)	0.2	0.6000 (-0.9166 to 2.1166)	0.1633
RAMRIS (Erosion)	0.0000 (-0.1192 to 0.1192)	0	0.1600 (-0.4781 to 0.7981)	0.5174
RAMRIS (Total)	0.4800 (-0.5389 to 1.4989)	0.1944	0.3200 (-1.5095 to 2.1495)	0.072
V_MRI	-3.1928 (-6.8886 to 0.5031)	-0.3286	2.4324 (-4.5521 to 9.4170)	0.1324
CRP	-2.0036 (-2.9520 to -1.0552)	-0.8191	-1.9224 (-3.1361 to -0.7087)	-0.6024
ESR	-39.6552 (-51.2945 to -28.0159)	-1.2959	-40.0345 (-53.8732 to -26.1957)	-1.100
TJC	-3.3043 (-4.8875 to -1.7212)	-0.9025	-4.0000 (-5.8622 to -2.1378)	-0.9288
SJC	-1.6087 (-2.6080 to -0.6094)	-0.6961	-1.9565 (-3.2569 to -0.6561)	-0.6506

VAS	-16.3478 (-29.1012 to -3.5945)	-0.5543	-24.7391 (-39.5955 to -9.8827)	-0.7200
DAS28-ESR	-1.8804 (-2.3562 to -1.4046)	-1.7089	-2.3265 (-2.8374 to -1.8156)	-1.9692

Table 4 Mean change with 95% confidence intervals (CI), standardized response means (SRM) for all measures at 2 and 5 months

See Table 1 for abbreviations

	Bone Score of Radiography at 1year	∆ Bone Score of Radiography	Bone Score of MR at 1year	∆ Bone Score of MR
DAS 28-ESR	0.5543	-0.0729	-0.4887	0.3523
	-0.06836 to 0.8662	-0.6446 to 0.5511	0.8704 to 0.2597	-0.4071 to 0.8237
	0.0768	0.8313	0.1819	0.3524
	11	11	9	9
JGPD-10	0.2673	0.3618	0.08901	0.3796
	-0.3068 to 0.6988	-0.2089 to 0.7487	-0.4858 to 0.6101	-0.2167 to 0.7696
	0.3556	0.2037	0.7725	0.2008
	14	14	13	13
JIPD-10	0.1735	0.4468	0.8807	0.5573
	-0.3933 to 0.6447	-0.1099 to 0.7901	-0.5179 to 0.5824	0.009123 to 0.8479
	0.5531	0.1093	0.8807	0.0478
	14	14	13	13
RAMRIS	0.3116	0.4107	0.9144	-0.01112
(total)	-0.2890 to 0.7362	-0.1814 to 0.7842	0.7324 to 0.9744	-0.5587 to 0.5432
	0.3	0.1634	<0.0001	0.9712

	13	13	13	13
RAMRIS	0.3406	0.1719	0.1232	0.2992
(synovitis)	-0.2590 to 0.7507	-0.4188 to 0.6603	-0.4589 to 0.6313	-0.3015 to 0.7299
	0.2547	0.5745	0.6884	0.3207
	13	13	13	13
RAMRIS	0.338	0.6476	0.9925	-0.04172
(bone erosion)	-0.2617 to 0.7494	0.1503 to 0.8834	0.9744 to 0.9978	-0.5794 to 0.5213
	0.2587	0.0167	<0.0001	0.8924
	13	13	13	13
RAMRIS	0.01461	0.4957	0.2642	0.2992
(bone edema)	-0.5407 to 0.5611	-0.07607 to 0.8221	-0.3356 to 0.7116	-0.3015 to 0.7299
	0.9622	0.085	0.383	0.3207
	13	13	13	13
V_MRI	-0.427	0.3728	-0.0942	0.3668
	-0.7807 to 0.1340	-0.1967 to 0.7542	-0.6134 to 0.4817	-0.2308 to 0.7635
	0.1279	0.085	0.7594	0.2176
	14	14	13	13

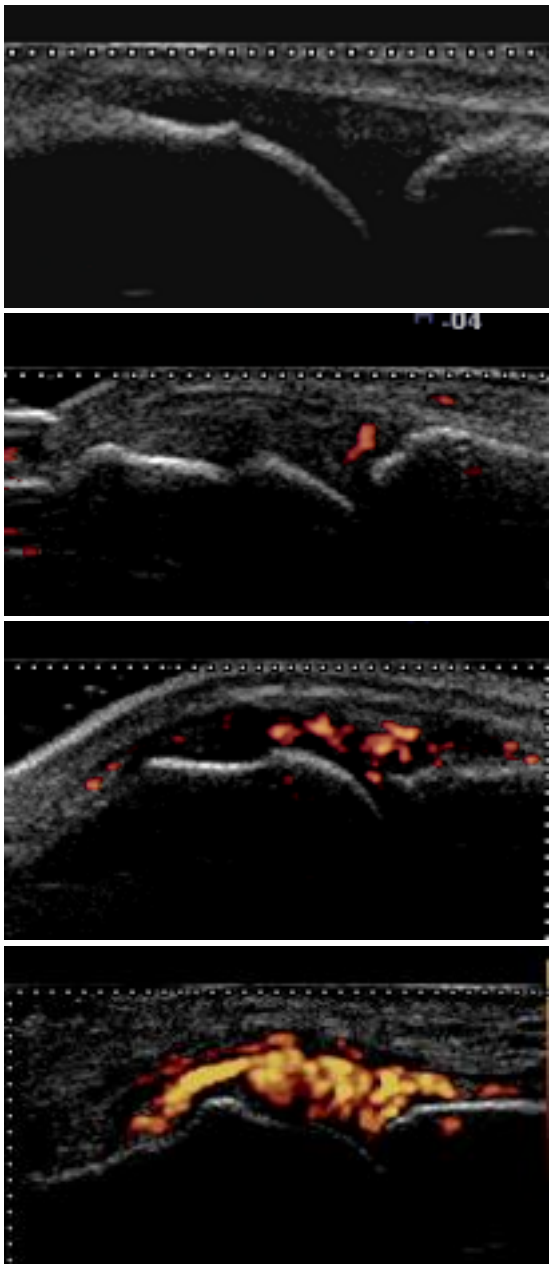
Table 5 Correlation between time-integrated values of clinical and imaging variables and bone damage progression

∆ means difference in value between baseline and 1-year follow-up.

From top to bottom, values are the median, range, 1st quartile and number of patients included.

See Table 1 for abbreviations.

Figures and Figure Captions



Grade 0

Grade 1

Grade 2

Grade 3

Figure 1 Power Doppler images corresponding to the image grading criteria for intra-articular vascularization: 0, absence of signal; 1, single vessel dots; 2, vessel dots over less than half the synovial area; 3, vessel dots over more than half the synovial area

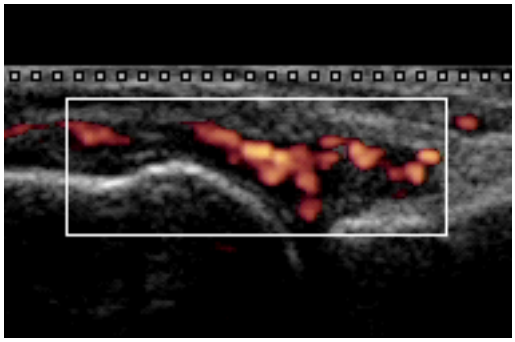


Fig. 2 32-year-old woman with rheumatoid arthritis. Quantitative power Doppler index (QPDI) analysis for 2nd metacarpophalangeal joint of the left finger are shown. When a rectangular region of interest (ROI) of 10 × 5 mm is selected (white box), the number of pixels in the whole ROI (7007 pixels) and the number of pixels with a positive Doppler signal (namely QPDI of 1395 pixels) automatically appears on the screen. This image corresponds to Grade 3 in the conventional power Doppler grading (vessel dots over more than half the synovial area).



Fig. 3a—ROI placement for muscle signal measurement

An approximately 30-mm^2 ROI was placed on the adductor pollicis muscle on this

STIR coronal image of the left hand. Mean ± standard deviation (range) of the muscle signal intensity was 62.8 ± 9.9 (31-92).

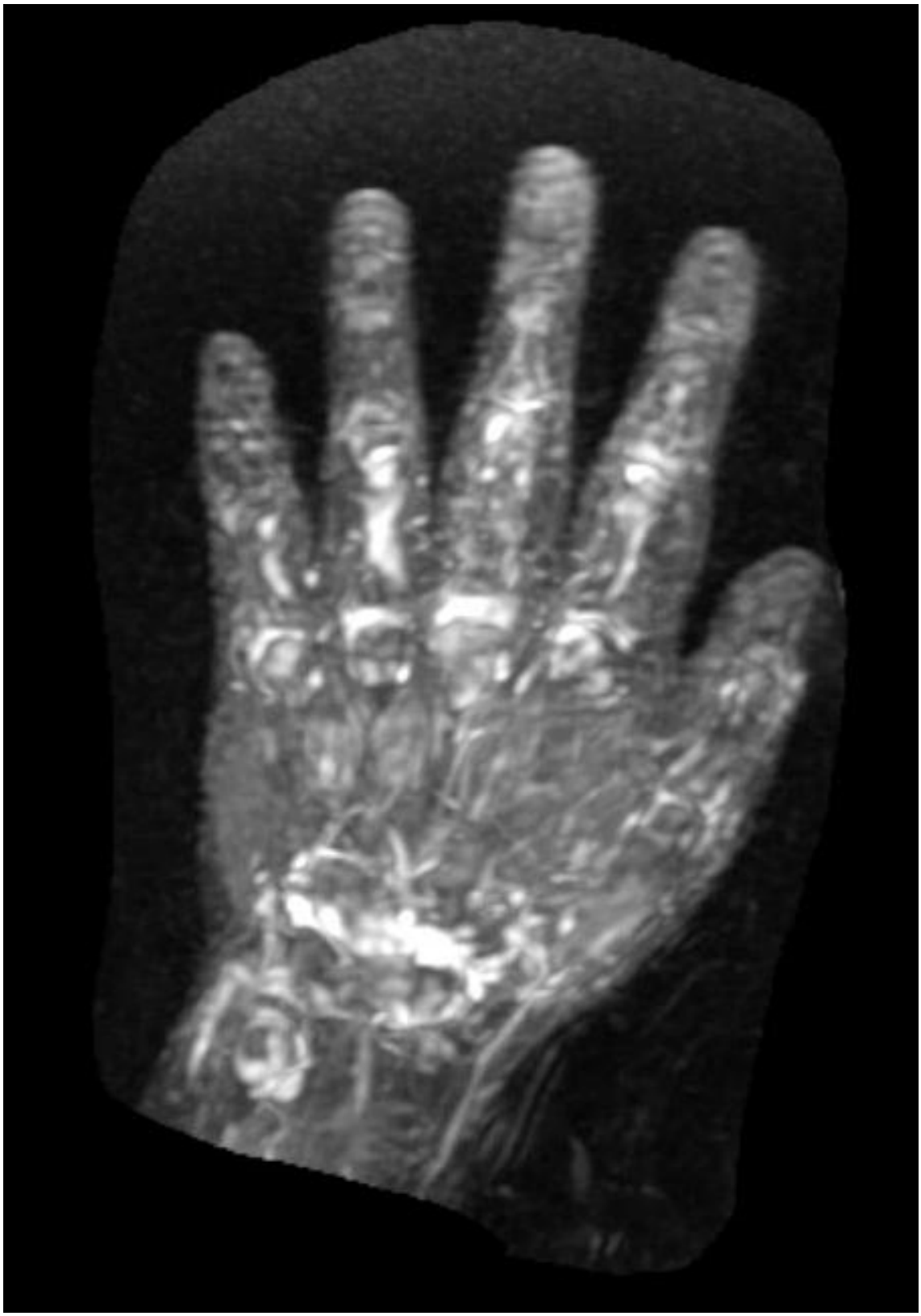


Fig. 3b—Representative 3D STIR image of the left hand.

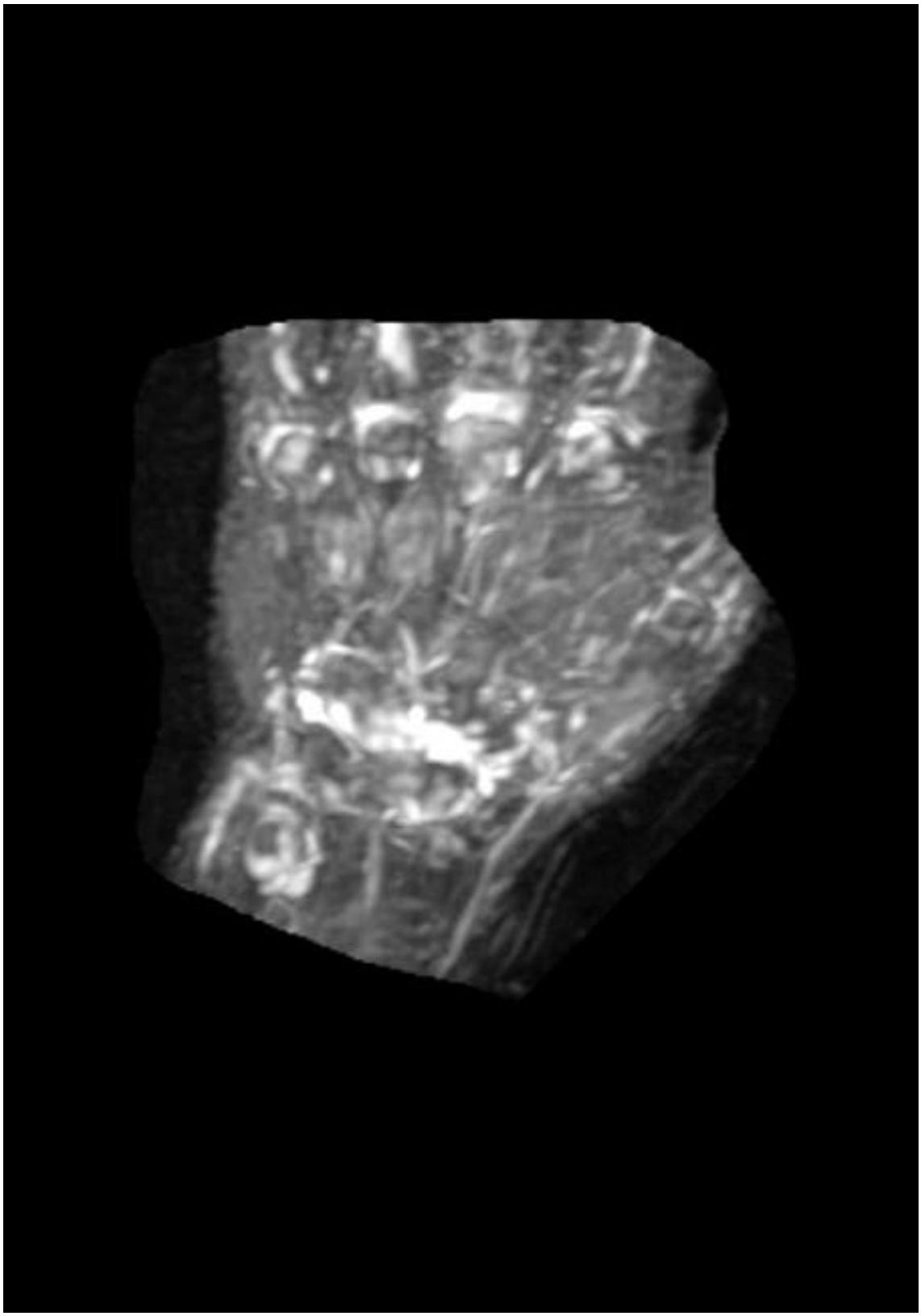


Fig. 3c—Representative 3D image to show the region of interest (ROI) setting for volumetry.

The volume of the MR signal was measured for wrists and MCP joints (distal ulna, distal radius, carpal bones, metacarpal bones, 1-5 metacarpophalangeal joints, and soft tissue); 1 cm proximal to the wrist joints and 1 cm distal to the MCP joints. By observing 2D and 3D images side by side, multiple slices were assessed on 2D images while contouring the ROI on 3D images to ascertain that the ROI was set appropriately.

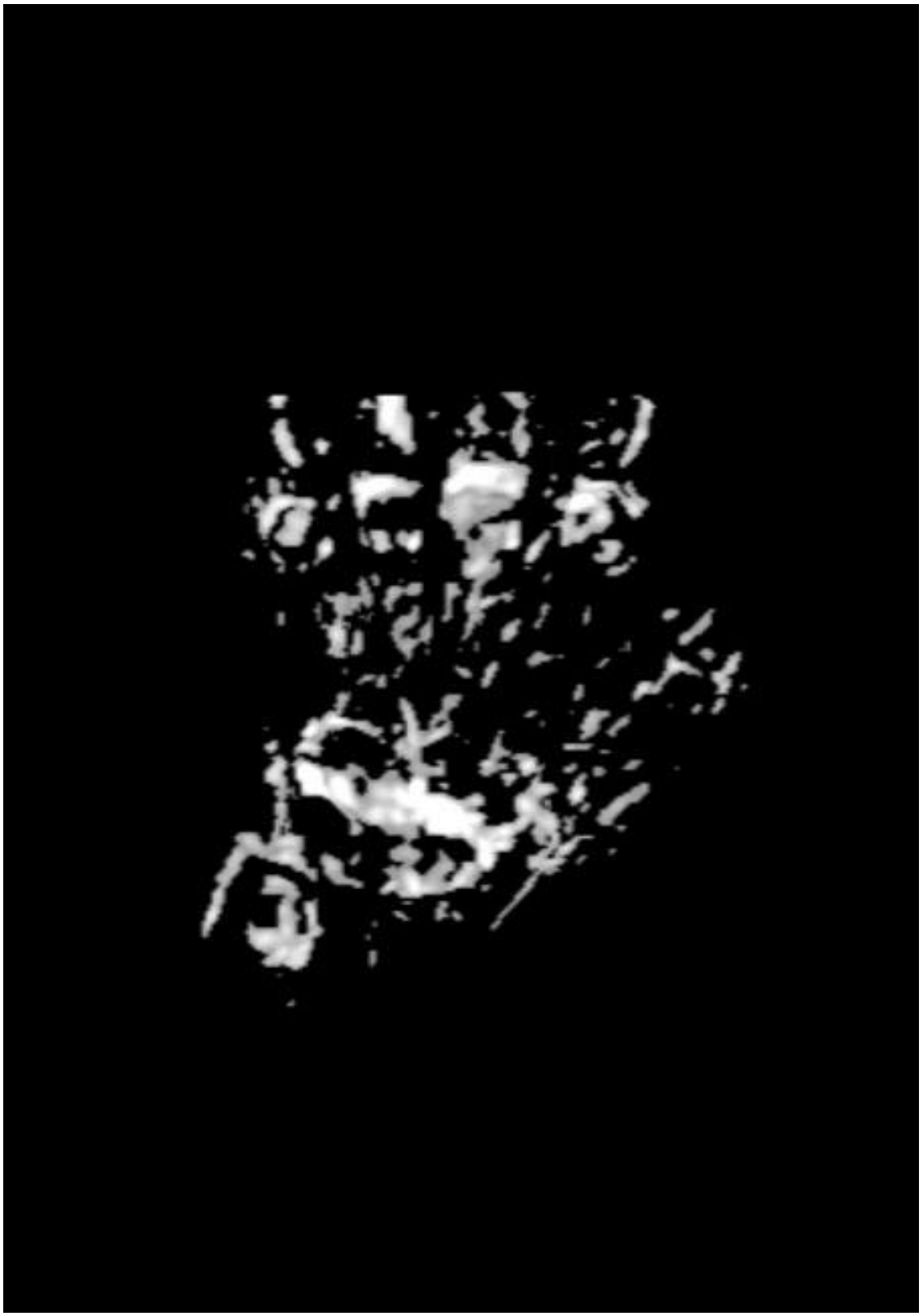


Fig. 3d—Volumetry applying threshold.

One point five (1.5) times the muscle signal (for this representative case, 94.2 (= 62.8 × 1.5)) was applied to the region of interest (ROI), resulting in volumes of 11.8 cc. The threshold for the 3D STIR image was determined according to the previous study to define the optimal threshold based on the muscle signal [25].

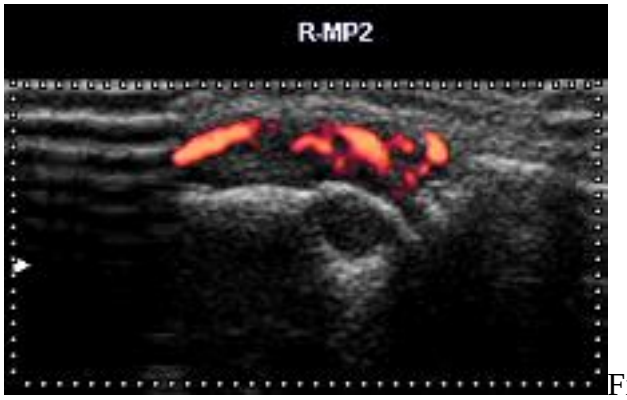


Figure 4a

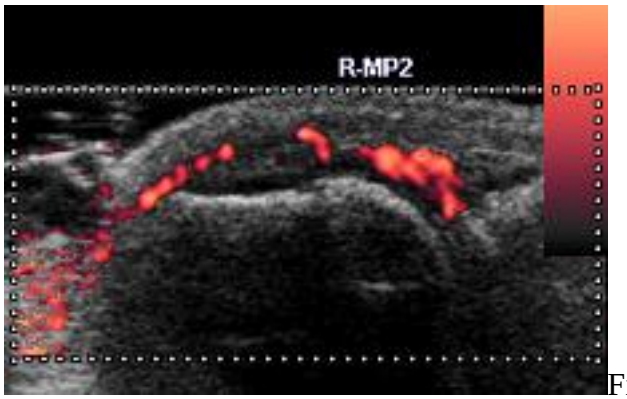


Figure 4b

Fig. 4—72-year-old man with rheumatoid arthritis.

Power Doppler images of the 2nd metacarpophalangeal joint of the right finger at baseline (Figure 4a) and 5 month follow-up (Figure 4b) study are shown. Both of these images correspond to Grade 3 in the conventional power Doppler grading (vessel dots over more than half the synovial area).When a rectangular region of interest (ROI) of 10 × 5 mm was selected (white dotted box), the numbers of pixels with a positive Doppler signal were 40 at the baseline (Figure 4a) and 29 at the 5-month follow-up (Figure 4b). This is an example to show that quantitative power Doppler analysis is more sensitive to therapeutic change than semi-quantitative analysis.

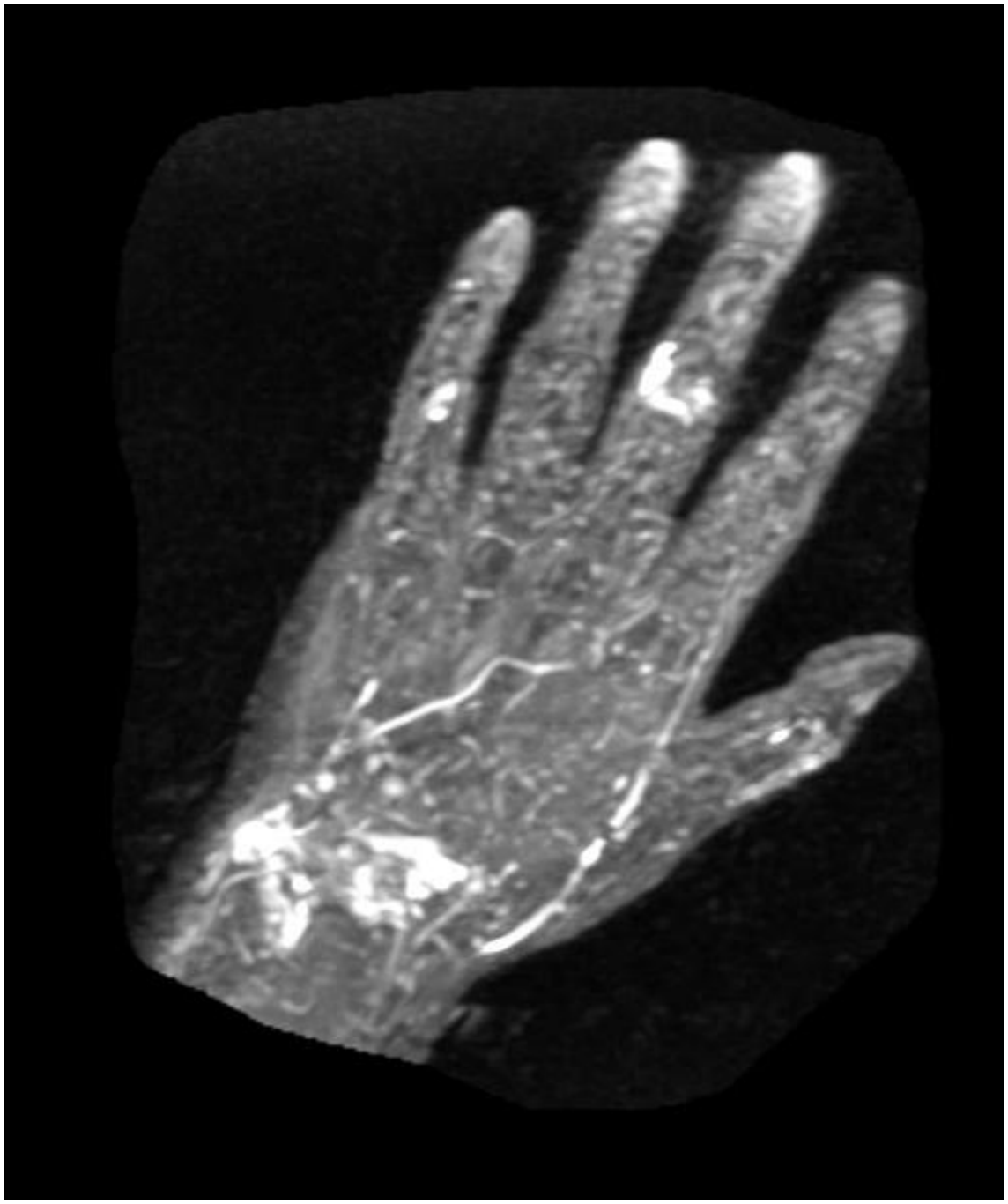


Fig. 5a

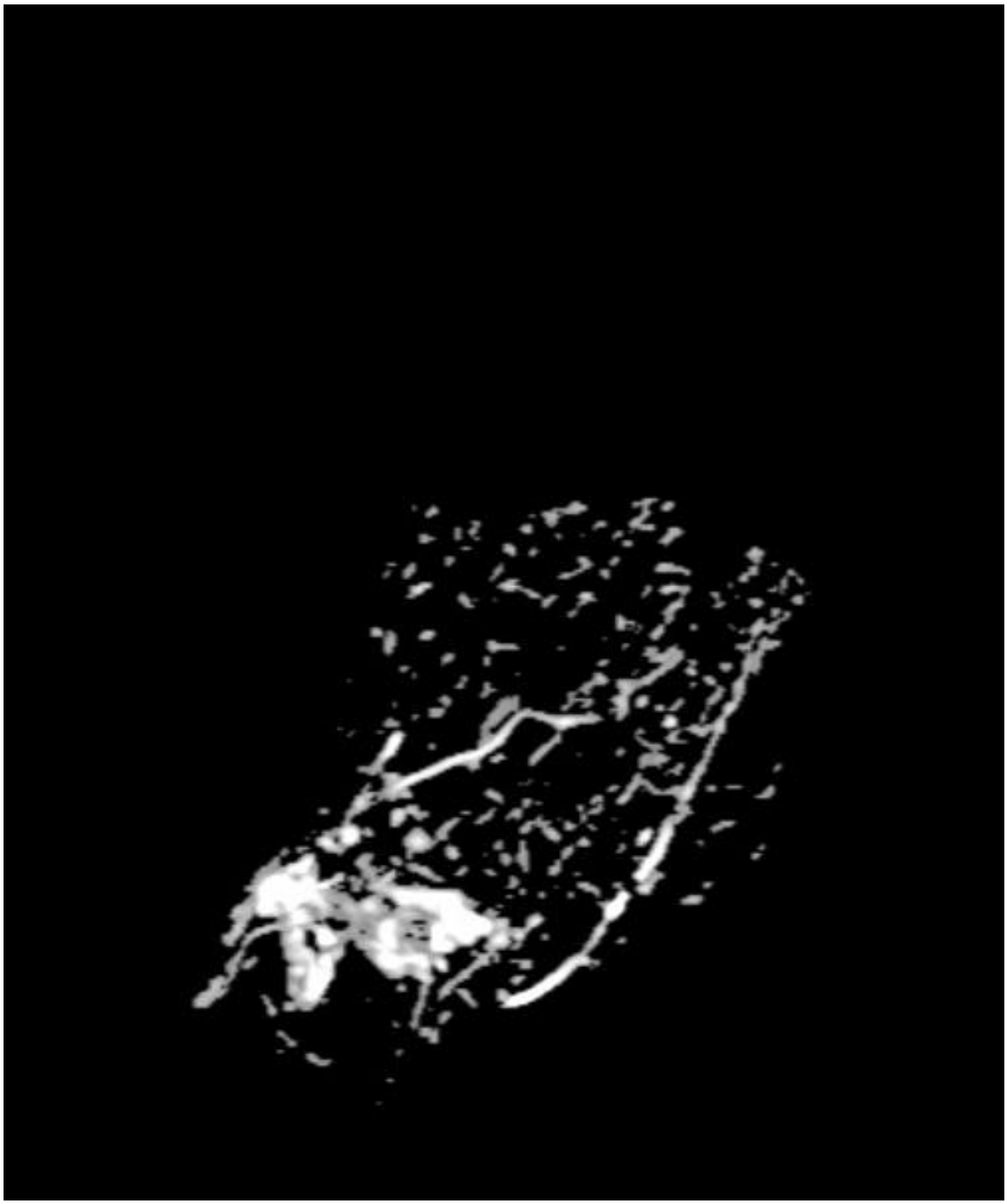


Fig. 5b

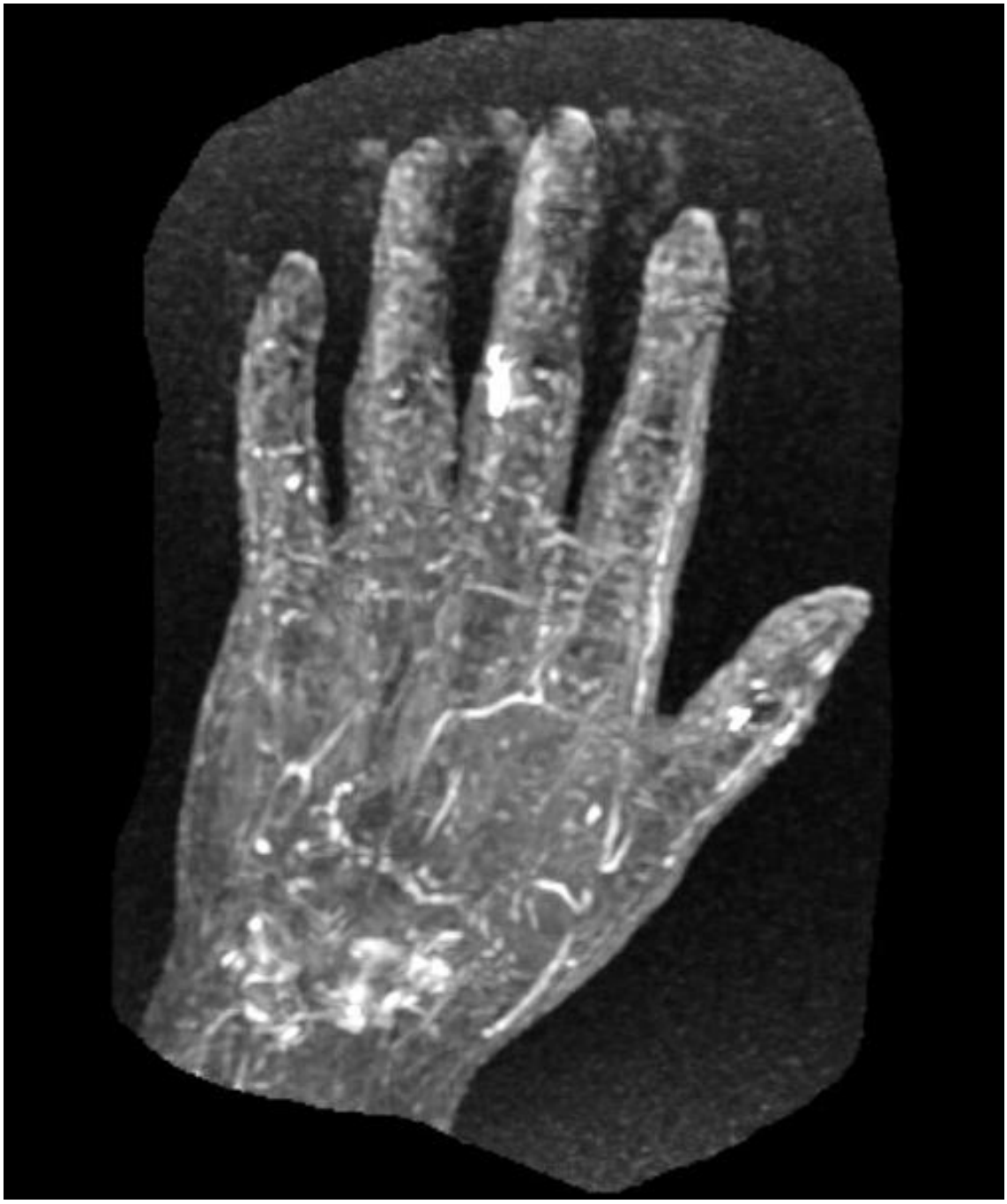


Fig. 5c



Fig. 5d

Fig.5—72-year-old woman with rheumatoid arthritis.

3D STIR images and V_ MRI for the left hand at baseline (Figure 5a and 5b) and at 5-month follow-up (Figure 5c and 5d) are shown. An abnormally high signal is seen in the wrist region of 3D STIR images at both the baseline (Figure 5a) and follow-up (Figure 5c). V_MRI was 14 cm3 for the baseline (Figure 5b) and 5 cm3 at the follow-up (Figure 5d), representing reduction of the inflammatory process after therapy.